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Signed Andrew Gerry

Dated 12 February 2002

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Request for grant of a patent

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The Patent Office
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1.	Your reference	4-31953P1
2.	Patent application number *(The Patent Office will fill in this part)*	0108876.4 P1 E620755-1 D00524 P00 0.00-0108876.4
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG SCHWARZWALDALLEE 215 4058 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487001
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	11
Claim(s)	3
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
~~Translations of priority documents~~	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co. Date: 09 April 2001

12. Name and daytime telephone number of person to contact in the United Kingdom: Mrs. E. Cheetham 020 8560 5847

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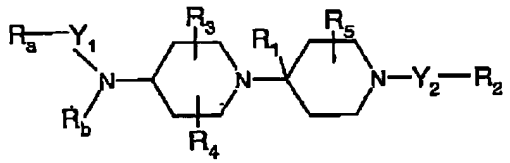
Organic Compounds

The present invention relates to piperidine derivatives, process for their production and pharmaceutical compositions containing them.

More particularly, the present invention provides a compound of formula I



I

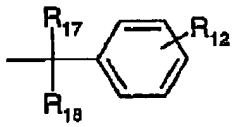
wherein

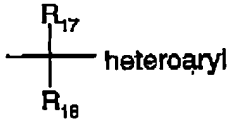
Y_1 is O; CH_2; or a direct bond;

Y_2 is –CO-; -CS-; -CO-NR_6-; -CS-NR_6-; -CO-O-; or –SO_2-;

R_1 is H; C_{1-6}alkyl; C_{2-6}alkenyl; or phenyl;

R_2 is phenyl, 6-membered heteroaryl, or 6-membered heteroaryl N-oxide, each being substituted by R_7, R_8 and R_9; R_{10}, R_{11}-substituted 5-membered heteroaryl; naphthyl;



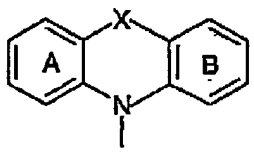
fluorenyl; diphenylmethyl; 

or ;

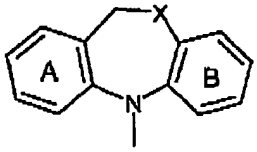
each of R_3, R_4 and R_5, independently, is H; or C_{1-6}alkyl; and

each of R_a and R_b, independently, is substituted or unsubstituted aryl or heteroaryl; or

R_a and R_b form together with the nitrogen to which they are bound a radical of formula (a) or (b)



(a) or



(b)

R_6 is H; or C_{1-4}alkyl;

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each of R_7 and R_8, independently, is halogen; C_{1-6}alkyl; $NR_{20}R_{21}$; OH; CF_3; OCH_3; -O-acyl; and OCF_3;

R_9 is R_7; H; phenyl; NO_2; CN; CH_2F; CHO; $-CH=NOR_{20}$; pyridyl; pyridyl N-oxide; pyrimidinyl; pyrazinyl; $-N(R_{20})CONR_{21}R_{22}$; -NHCONH(chloro-$C_{1-6}$alkyl); -NHCONH($C_{3-10}$cycloalkyl)($C_{1-6}$alkyl); -NHCO($C_{1-6}$alkyl); $-NHCOCF_3$; $-NHSO_2N(C_{1-6}alkyl)_2$; $-NHSO_2C_{1-6}$alkyl; $-N(SO_2CF_3)_2$; $-NHCO_2(C_{1-6}alkyl)$; C_{3-10}cycloalkyl; $-SR_{23}$; $-SOR_{23}$; $-SO_2NH(C_{1-6}alkyl)$; $-OSO_2(C_{1-6}alkyl)$; OSO_2CF_3; hydroxy-C_{1-6}alkyl; $-CONR_{20}R_{21}$; $-CON(CH_2CH_2-O-CH_3)_2$; -OCONH(C_{1-6}alkyl); $-CO_2R_{20}$; $-Si(CH_3)_3$ or $-B(OC(CH_3)_2)_2$;

R_{10} is C_{1-6}alkyl; NH_2; or R_{12}-phenyl;

R_{11} is H; or C_{1-6}alkyl;

R_{12} is 1 to 3 substitutents independently selected from the group consisting of H; C_{1-6}alkyl; CF_3; $-CO_2R_{20}$; CN; C_{1-6}alkoxy; and halogen;

each of R_{17} and R_{18}, independently, is H; C_{1-6}alkyl; or R_{17} and R_{18} together are C_{2-5}alkylene and with the carbon atom to which they are attached form a spiro ring of 3 to 6 carbon atoms;

each of R_{20}, R_{21} and R_{22}, independently, is H or C_{1-6}alkyl;

R_{23} is C_{1-6}alkyl; or phenyl;

X is O; $-NR_c-$ wherein R_c is H or C_{1-4}alkyl; S; or CH_2;

each of ring A and B, independently is optionally substituted;

in free form or in salt form.

Halogen may be fluoro, chloro, bromo or iodo.

Acyl is a radical of a carboxylic acid of formula (C_{1-6}alkyl)-CO-, aryl-CO-, ar-C_{1-6}alkyl-CO-, C_{3-7}cycloalkyl-CO-, C_{3-7}cycloalkyl-C_{1-6}alkyl-CO-, or heteroaryl-CO- wherein aryl or heteroaryl is as defined herein.

Aryl may be R_{12}-phenyl; R_{12}-naphthyl; or R_{12}-tetrahydronaphthyl.

By heteroaryl is meant a five or six membered saturated, unsaturated or aromatic heterocyclic or heterobicyclic ring optionally substituted and comprising 1 or 2 heteroatoms, independently selected from N, O and S, provided that the rings do not contain adjacent oxygen and/or sulfur atoms. Nitrogen atoms can form an N-oxide. For 6-membered heteroaryl rings, carbon atoms can be substituted by R_7, R_8 or R_9 groups. For 5-membered

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heteroaryl rings, carbon atoms may be substituted by R_{10} or R_{11} groups. Suitable examples include e.g. furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidinyl or pyridazinyl. Bicyclic rings are benzo-fused ring systems derived from the heteroaryl groups named above, e.g. quinolyl, phtalazinyl, quinazolinyl, benzofuranyl, benzothienyl or indolyl.

The compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid when R_2, R_a and/or R_b comprises an optionally substituted amino group or a heterocyclic residue which can form addition salts. When the compounds of formula I have one or more asymetric centers in the molecule, e.g. when a piperidin ring is substituted, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof.

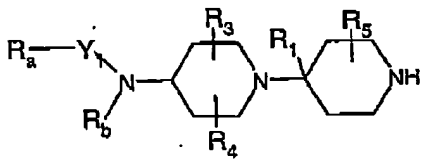
When ring A or B is substituted, carbon atoms can be substituted by R_7, R_8 or R_9 groups. X is preferably O, S or CH_2.

Preferably each of R_a and R_b is substituted or unsubstituted aryl, e.g. phenyl substituted by F, Br or CF_3, preferably monosubstituted, or unsubstituted phenyl. When aryl as R_a or R_b is monosubstituted, the substitutent is preferably in para.

Preferably R_1 is CH_3. Each of R_3, R_4 and R_5 preferably is H.
Preferably R_2 is a phenyl, pyridyl, pyrazyl, pyridine-N-oxide or pyrazyl-N-oxide group, each being optionally mono- or disubstituted, e.g. by methyl, R_a being H. Y_2 is preferably –CO-.

The present invention also includes a process for the preparation of a compound of formula I which process may comprise

a) reacting a compound of formula II



II

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wherein R_a, R_b, R_1, and R_3 to R_5 are as defined above,
with a compound of formula III

$$R_2 - Y_{2a} \qquad III$$

wherein R_2 is as defined above, and Y_{2a} is -COOH, $-NR_6$-COCl, -O-CO-Cl, $-SO_2$-Cl, or a functional derivative thereof; or

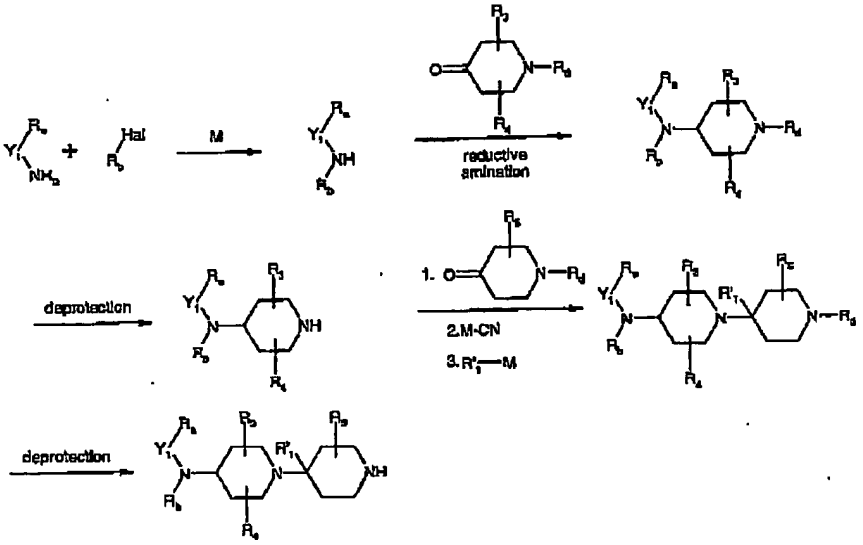
b) linking together the R_a-Y_1-NR_b- fragment with the remaining bipiperidinyl fragment, the 2 fragments being such that the desired compound of formula I is obtained; or

c) linking together 2 substituted piperidine fragments in such a way that the desired compound of formula I is obtained,

and, where required, converting the resulting compound of formula I obtained in free form into the desired salt form, or vice versa.

The reaction steps a), b) or c) may be performed in accordance with methods known in the art or as disclosed in the Examples below.

Compound of formula II, used as starting material, may be prepared as follows:



wherein R_a, R_b, R_3 to R_5 and Y_1 are as defined above, R'_1 is other than H, M is a metal which may be charged e.g. Pd^{++} or Mg^{++} and/or linked to a further group, e.g. CH_3-CO_2^- or

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Br^-, and R_d is an amino protecting group, e.g. as disclosed in "Protective Groups in Organic Synthesis" T.W. Greene, J.Wiley & Sons NY, 2nd ed., chapter 7, 1991, and references therein, e.g. tert.-butoxy-carbonyl, benzyloxycarbonyl or 9-fluorenyl methoxy carbonyl.

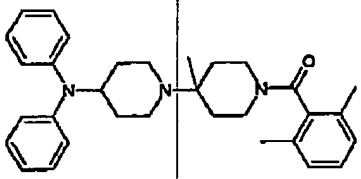
Compounds of formula II wherein R_1 is H, may be obtained by following the same procedure as disclosed above, except that steps 2 and 3 are suppressed and step 1 is a reductive amination. Compounds of formula II may also be prepared by linking together the R_e-Y_1-NR_b- fragment with the remaining amino protected bipiperidinyl fragment.

Above reactions may be carried out in accordance with methods known in the art or as disclosed hereafter.

Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as described hereafter.

The following Examples are illustrative of the invention.

Example 1: (2,6-Dimethyl-phenyl)-(4-diphenylamino-4'-methyl-[1,4']bipiperidinyl-1'-yl)-methanone



A mixture of (4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (0.25 g, 0.71 mmol), 2,6-dimethylbenzoic acid (0.32 g, 2.13 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.57 g, 1.5 mmol), $EtN(i\text{-}Pr)_2$ (0.6 ml) and DMF (5 ml) is stirred for 16 h at 20°C. The mixture is diluted with t-butyl methylether (25 ml), washed with 2N NaOH (25 ml) and brine (25 ml) and dried with sodium sulfate. The solvent is removed and the residue purified by chromatography (SiO_2, t-butyl methylether/cyclohexane 1:4→1:0). The title compound is isolated as a colorless solid. MS/ESI 482 $(M+H)^+$;

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^{1}H NMR (400 MHz, DMSO) δ= 0.89 (3 H, s), 1.14-1.25 (3 H, m), 1.39 (1 H, m), 1.59 (1 H, m), 1.75 (1 H, m), 1.83-1.95 (2 H, m), 2.01 (3 H, s), 2.13 (3 H, s), 2.11-2.24 (2 H, m), 2.85 (2 H, m), 2.95 (1 H, m), 3.01 (1 H, m), 3.35 (1 H, m), 3.70-3.83 (2 H, m), 6.77 (4 H, m), 6.92-7.05 (4 H, m), 7.12 (1 H, m), 7.26 (4 H, m).

(4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine, used as starting material may be prepared as follows:

a) A suspension of diphenyl-piperidin-4-yl-amine (1.26 g, 5.00 mmol), 1(t-butyl oxycarbonyl)-4-piperidone (1.00 g, 5.00 mmol), and titanium(IV) isopropoxide (1.42 g, 5.00 mmol) in 1,2-dichloroethane (25 ml) is stirred for 1 h at 80°C and then for 16 h at 20°C. Diethylaluminum cyanide (10 ml 1M solution in toluene) is added and the mixture stirred for additional 24 h. The solvent is removed and the crude material dissolved in tetrahydrofuran (25 ml). Methylmagnesium bromide (8.7 ml 3M solution in ether) is added dropwise and the mixture stirred for 3 h at 20°C. Ammonium chloride (10 % solution, 50 ml) and ethyl acetate (50 ml) are added, the organic phase washed with ammonium chloride (10 % solution, 50 ml) and sodium hydrogencarbonate (10 % solution, 50 ml), dried with sodium sulfate and the solvent removed. The residue is subjected to chromatography (SiO_2, ethyl acetate/cyclohexane 1:9→1:1). 4-Diphenylamino-4'-methyl-[1,4']bipiperidinyl-1'-carboxylic acid tert.-butyl ester is isolated as a colorless solid MS/ESI 450 $(M+H)^+$.

b) A mixture of trifluoroacetic acid (2 ml) and water (0.1 ml) is added dropwise to a solution of compound a) above (0.81 g, 1.80 mmol) in methylene chloride (5 ml) and the mixture stirred for 3 h at 20°C. Sodium hydrogencarbonate (10% solution, 10 ml) and ethyl acetate (20ml) are added and the organic phase dried with sodium sulfate. The solvent is removed and the residue sublected to chromatography (RP-18, methanol/H_2O 1:3→O:1). (4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine is isolated as a colorless oil. MS/ESI 350 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) □= 0.88 (3 H, s), 1.35 (4 H, m), 1.60 (4 H, m), 1.93 (2 H, m), 2.15 (2 H, m), 2.58 (2 H, m), 2.87 (2 H, m), 2.96 (2 H, m), 3.76 (1 H, m), 6.78 (4 H, m), 6.94 (2 H, m), 7.22 (4 H, m).

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The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g. as CCR5 antagonists, e.g. as indicated in in vitro tests and therefore indicated for therapy.

a) CCR5 membrane binding assay

A high throughput assay utilizes a CCR5 membranes assay to identify inhibitors of MIP-1□ binding. This assay uses membranes from CHO cells expressing human CCR5 chemokine receptor. MIP-1□ is a natural ligand for CCR5. In a 96-well plate format, using the Scintillation Proximity Assay (SPA) [Amersham Pharmacia Biotech], membranes are incubated with wheat germ agglutinin coated PVT beads, [I-125]labelled MIP-1α and either buffer or serial dilutions of the compound to be tested for 2 hours at room temperature. After centrifugation the plates are counted in a Topcount (Packard). The data are reported as IC_{50}, i.e. the concentration of compound required to achieve 50% inhibition of [I-125]MIP-1α binding. In this assay, compounds of formula I have an $IC_{50} \leq 1\mu M$.

b) CCR5 functional assay

Human CCR5 is used to generate stable transfectants in CHO K1 cells. These CCR5 transfectants are used for assessing Ca mobilization in response to stimulation by the CCR5 ligands MIP-1a, MIP-1b or RANTES. For the assay the cells are loaded with a Ca-sensitive fluorochrome (Fluo3 or Fluo4). Ligand concentrations between 0.01 - 10 nM are used to induce Ca mobilization which is monitored in a fluorometer with appropriate settings.

To assess the activity of the compounds to be tested, a baseline fluorescence reading is taken after which the compounds at the desired concentration are added to the cells and fluorescence is further recorded for a certain time to assess whether compounds show agonistic effects. Next the agonist is added to the mixture and fluorescence monitored. The inhibition of Ca flux in the presence of the compounds to be tested is calculated from the inhibition of maximal fluorescence induced by the agonist. IC_{50} values are calculated from dose-response curves obtained with the compounds. In this assay, compounds of formula I have an $IC_{50} \leq 1\mu M$.

The compounds of formula I are, therefore, useful in the prevention and/or treatment of diseases or disorders mediated by interactions between chemokine receptors and their

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ligands, e.g. in transplantation, such as acute or chronic rejection of organ or tissue allo- or xenografts or delayed graft function, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pernicious anemia, Sjoegren syndrome, uveitis, psoriasis, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock, others, cancer, e.g. solid tumors, T cell lymphomas, T cell leukemias, metastasizing or angiogenesis, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock, adult respiratory distress syndrome or viral infections, e.g. AIDS.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to10 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 500 mg active ingredient.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

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The compounds of formula I may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

1.1 A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.2 A method for preventing or treating acute or chronic transplant rejection or inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

2. A compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 or 1.2 above.

3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 or 1.2 above comprising a compound of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 or 1.2 above.

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. in immunosuppressive or immunomodulating regimens or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, a chemotherapeutic agent or an anti-infective agent, e.g. an anti-viral agent or an antibiotic. For example, the compounds of formula I may be used in combination with a

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disorders, a chemotherapeutic agent or an anti-infective agent, e.g. an anti-viral agent or an antibiotic. For example, the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a macrocyclic lactone having immunosuppressive properties, e.g. rapamycin or 40-O-(2-hydroxyethyl)-rapamycin (RAD); an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40. CD45, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y ; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory or chemotherapeutic therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I and at least a second drug substance, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic drug, e.g. as indicated above.

6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a compound of formula I as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant,

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immunomodulatory, anti-inflammatory or chemotherapeutic drug. The kit may comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

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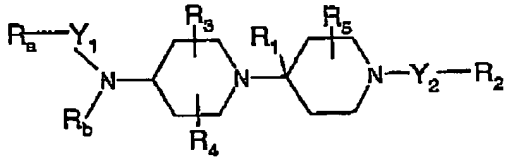
CLAIMS

1. A compound of formula I



I

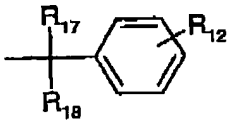
wherein

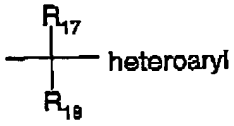
Y_1 is O; CH_2; or a direct bond;

Y_2 is –CO-; -CS-; -CO-NR_6-; -CS-NR_6-; -CO-O-; or $-SO_2$-;

R_1 is H; C_{1-6}alkyl; C_{2-6}alkenyl; or phenyl;

R_2 is phenyl, 6-membered heteroaryl, or 6-membered heteroaryl N-oxide, each being substituted by R_7, R_8 and R_9; R_{10}, R_{11}-substituted 5-membered heteroaryl; naphthyl;

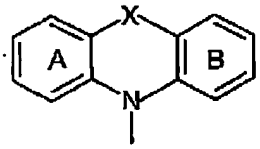


fluorenyl; diphenylmethyl;  or ;

each of R_3, R_4 and R_5, independently, is H; or C_{1-6}alkyl; and

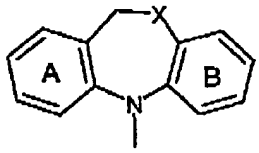
each of R_a and R_b, independently, is substituted or unsubstituted aryl or heteroaryl; or

R_a and R_b form together with the nitrogen to which they are bound a radical of formula (a) or (b)



(a)

or



(b)

R_6 is H; or C_{1-4}alkyl;

each of R_7 and R_8, independently, is halogen; C_{1-6}alkyl; $NR_{20}R_{21}$; OH; CF_3; OCH_3; -O-acyl; and OCF_3;

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R_9 is R_7; H; phenyl; NO_2; CN; CH_2F; CHO; -CH=NOR_{20}; pyridyl; pyridyl N-oxide; pyrimidinyl; pyrazinyl; -N(R_{20})CONH$R_{21}R_{22}$; -NHCONH(chloro-C_{1-6}alkyl); -NHCONH(C_{3-10}cycloalkyl)(C_{1-6}alkyl); -NHCO(C_{1-6}alkyl); -NHCOCF$_3$; -NHSO$_2$N(C_{1-6}alkyl)$_2$; -NHSO$_2C_{1-6}$alkyl; -N(SO_2CF_3)$_2$; -NHCO$_2$(C_{1-6}alkyl); C_{3-10}cycloalkyl; -SR_{23}; -SOR_{23}; -SO$_2$NH(C_{1-6}alkyl); -OSO$_2$(C_{1-6}alkyl); OSO$_2$CF$_3$; hydroxy-C_{1-6}alkyl; -CONH$R_{20}R_{21}$; -CON(CH_2CH_2-O-CH_3)$_2$; -OCONH(C_{1-6}alkyl); -CO$_2R_{20}$; -Si(CH_3)$_3$ or –B(OC(CH_3)$_2$)$_2$;

R_{10} is C_{1-6}alkyl; NH_2; or R_{12}-phenyl;

R_{11} is H; or C_{1-6}alkyl;

R_{12} is 1 to 3 substitutents independently selected from the group consisting of H; C_{1-6}alkyl; CF_3; -CO$_2R_{20}$; CN; C_{1-6}alkoxy; and halogen;

each of R_{17} and R_{18}, independently, is H; C_{1-6}alkyl; or R_{17} and R_{18} together are C_{2-5}alkylene and with the carbon atom to which they are attached form a spiro ring of 3 to 6 carbon atoms;

each of R_{20}, R_{21} and R_{22}, independently, is H or C_{1-6}alkyl;

R_{23} is C_{1-6}alkyl; or phenyl;

X is O; -NR_c- wherein R_c is H or C_{1-4}alkyl; S; or CH_2;

each of ring A and B, independently is optionally substituted;

in free form or in salt form.

2. A compound of formula I substantially as herein defined and described.

3. A compound of formula I according to claim 1 or 2, or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.

4. A pharmaceutical composition comprising a compound of formula I according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier therefor.

5. A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, e.g. as described herein, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

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6. A method according to claim 5 comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I according to claim 1 or 2 or a pharmaceutically acceptable salt thereof and at least a second drug substance.

7. A compound of formula I according to claim 1 or 2 or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as defined in claim 5.

8. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a compound of formula I according to claim 1 or 2 or a pharmaceutically acceptable salt thereof, and b) at least one co-agent.

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